Notice of Allowability	Application No.	Applicant(s)	
	10/766,102	SCHNABLE ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are *21-25,27 and 30-33*.

3. ☒ The drawings filed on *08 November 2004* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 5/5/05
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

5.00

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with M. Angela Parsons on 7/25/05.

The application has been amended as follows:

In the title:

The title has been replaced with the following:

-- METHOD OF IDENTIFYING AN OPEN READING FRAME USING A NUCLEIC ACID MOLECULE ENCODING MULTIPLE START CODONS AND HISTIDINE TAGS --

In the specification:

Paragraph beginning at page 5, line 4, has been amended as follows:

The invention provides an isolated nucleic acid that encodes three start codons; each start codon is located within one of the three reading frames. The start codons can be ATG codons and can be found within a span of 50 nucleotides. In one embodiment, the nucleic acid encoding the three start codons has the sequence 5' ATGGCATGGCATG 3' (SEQ ID [NO. 19] NO:18). The isolated nucleic acid that encodes the three start codons also can have a ribosome-binding site positioned 5' of the start codons.

Paragraph beginning at page 5, line 10, has been amended as follows:

In another embodiment, the invention provides for a vector that has a portion that encodes three start codons, one in each reading frame. The start codons can be ATG codons that occur within a span of 13 nucleotides, and more specifically, the 13 nucleotides can have the sequence 5' ATGGCATGGCATG 3' (SEQ ID [NO. 1] NO:18). Furthermore, the vector that has a portion encoding three start codons also can have a portion that encodes histidine tags in three reading frames. In addition, a ribosome-binding site can be positioned 5' of the start codons. One or more cloning sites can be located 3', 5', or 3' and 5' of the portion encoding histidine tags to facilitate cloning. The vector can be, for example, the pHis6 vector.

Paragraph beginning at page 6, line 12, has been amended as follows:

In another embodiment, the invention provides an isolated nucleic acid having the sequence of SEQ ID [NO. 16] NO:15.

Paragraph beginning at page 6, line 14, has been amended as follows:

In another embodiment, the invention provides an isolated nucleic acid having the sequence of SEQ ID [NO. 17] NO:16.

Paragraph beginning at page 6, line 29, has been amended as follows:

Figure 1 is a diagrammatic illustration of the 3-frame His-tag coding sequence and its location within the structure of the pHis4 vector. The 3-frame His-tag coding region is 93 base pairs in length and spans the region of nucleotides 196 to 283 (SEQ ID NOs:1, 21, 24, and 26, where SEQ ID NO:26 is the complementary strand). The protein translation for each of the three frames is shown below the nucleic acid sequence (SEQ ID NOs:20 (frame 1), 22-23 (frame 2), and 25 (frame 3)). Poly-histidine residues comprising the histidine tag of each reading frame are shown in bold. The MCS is located 5' to the 3-frame his-tag coding sequence at nucleic acid positions 283 to 299. The arrow indicates the direction of translation. The T7 promoter, used for expression of a protein that is cloned 3' of the MCS, is located at positions 299 to 402. Nucleotides 403-631 contain the 5' untranslated region of the *E. coli* ompA gene, obtained from the plasmid pTrip1EX, while the remaining region of the pHis4 plasmid, nucleotides 632-4603 and nucleotides 1-196, is derived from the pZL1 plasmid.

Paragraph beginning at page 7, line 25, has been amended as follows:

Figure 5A is the sequence of part of the T7 promoter, the ribosome binding site, and the triple-ATG sequence in the ORF Rescue vector (SEQ ID NO:17).

Paragraph beginning at page 7, line 27, has been amended as follows:

Figure 5B is a diagrammatic illustration of the ORF Rescue vector, pHis6. The 3-frame His-tag coding region is 118 base pairs in length (SEQ ID NOs:27, 30, 34, and 37, where SEQ ID NO:37 is the complementary strand). The protein translation for each of the three frames is shown below the nucleic acid sequence (SEQ ID NOs:28-29 (frame 1), 31-33 (frame 2), and 35-36 (frame 3)).

Paragraph beginning at page 9, line 12, has been amended as follows:

The nucleotide sequences of the invention allow for the translation of a histidine tag regardless of the reading frame used in the gene sequence that is upstream or downstream of the 3-frame His-tag DNA sequence. That is, the triplet code is capable of encoding histidine residues in any of the three reading frames. This is illustrated in the following example.

Although many sequences can code for three or more histidine residues in all three reading frames, the following sequence is illustrative:

5' AAG CTT CAC CAC CAT CAT CAT CAC GCA TCA CCA CCA CCA CCA CGC ATC ATC ATC ACC ATC ACC TCG AGC GTC ACA CTA GCT GAG TAA GCA TGC 3' (SEQ ID NO:1)

Paragraph beginning at page 9, line 23, has been amended as follows:

In the first reading frame, i.e., if the first nucleotide in this sequence is considered the first nucleotide position of a codon, the translation of this sequence will be:

5' AAG CTT CAC CAC CAT CAT CAT CAC GCA TCA CCA CCA CCA
K L H H H H H H A S P P P

CCA CGC ATC ATC ATC ACC ATC ACC TCG AGC GTC ACA CTA GCT
P R I I I T I T S S V T L A

GAG TAA GCA TGC 3' (SEQ ID NO:1)
E * A C (SEQ ID NO:20)

Paragraph beginning at page 10, line 1, has been amended as follows:

In the second reading frame, i.e., if the second nucleotide in this sequence is considered the first nucleotide position of a codon, the translation of this sequence will be:

5' A AGC TTC ACC ACC ATC ATC ATC ACG CAT CAC CAC CAC CAC
S F T T I I I T H H H H H

CAC GCA TCA TCA TCA CCA TCA CCT CGA GCG TCA CAC TAG CTG
H A S S S P S P R A S H * L

AGT AAG CAT GC 3' (SEQ ID NO:21)
S K H (SEQ ID NOs:22 and 23)

Paragraph beginning at page 10, line 13, has been amended as follows:

And finally, in the third reading frame, i.e., if the third nucleotide in this sequence is considered the first nucleotide position of a codon, the translation of this sequence will be:

5' AA GCT TCA CCA CCA TCA TCA TCA CGC ATC ACC ACC ACC ACC
A S P P S S S R I T T T T

ACG CAT CAT CAT CAC CAT CAC CTC GAG CGT CAC ACT AGC TGA
T H H H H H H L E R H T S *

GTA AGC ATG C 3' (SEQ ID NO:24)
V S M (SEQ ID NO:25)

Paragraph beginning at page 22, line 1, has been amended as follows:

The His-tag DNA sequence 1 (SEQ ID NO:1) has *Hin*dIII and *Sph*I sites at the 5' and 3' ends, respectively. They are used for cloning into a vector. SEQ ID NO:1 has the following sequence:

5' AAG CTT CAC CAC CAT CAT CAT CAC GCA TCA CCA CCA CCA CCA CGC ATC ATC ATC ACC ATC ACC TCG AGC GTC ACA CTA GCT GAG TAA GCA TGC 3' (SEQ ID NO:1)

Paragraph beginning at page 22, line 7, has been amended as follows:

For cloning into a vector, the His-tag DNA sequence 2 (SEQ ID NO:2) was synthesized with *Kpn*I and *Xho*I sites at the 5' and 3' ends respectively. SEQ ID NO:2 has the following sequence:

5' GTA CCC ACC ACC ATC ATC ATC ACG CAT CAC CAC CAC CAC CAC GCA TCA TCA TCA CCA TCA CCT CGA 3' (SEQ ID NO:2)

Paragraph beginning at page 22, line 12, has been amended as follows:

b. Sequences of the PCR primers and linkers used in vector constructions

Linker 1a: 5' CTG CAG CGG CCG CG 3' (SEQ ID NO:3)

Linker 1b: 5' CTA GGC GCC GGC GAC GTC TCG A 3' (SEQ ID NO:4)

Linker 2a: 5' CTA GCT GCA GAT ATC A 3' (SEQ ID NO:5)

Linker 2b: 5' AGC TTG ATA TCT GCA G 3' (SEQ ID NO:6)

ZL2: 5' CCA TCG ATC CGA GAT AGG GTT GAG T 3' (SEQ ID NO:7)

HTI : 5' ACG AGC TCA GGC AGA GAC GA 3' (SEQ ID NO:8)

HT2: 5' ACG AGC TCG CAG AGA CGA CG 3' (SEQ ID NO:9)

ZL1: 5' CCT CGA GTC ACA CAG GAA ACA GCT AA 3' (SEQ ID NO:10)

ZL3: 5' GGC TAG CAG CTG TTT CCT GTG TGA 3' (SEQ ID NO:11)

ZL4: 5' GTG GAG CAT CTG GTC GCA 3' (SEQ ID NO:12)

ZL8: 5' GAG ATC TGC CAT AAC ATG TCA TCA TAG CTG TTT CCT G 3' (SEQ ID NO:13)

ZL10: 5' GAG ATC TGC CAT AAC ATG TCA TCA TAG CTG TTT CCT G 3' (SEQ ID NO:[14] 13)

T7 Linker: 5' CTA GCC GAA ATT AAT ACG ACT CAC TAT AGG GAG AC 3' (SEQ ID NO:[15] 14)

pHis6L: 5' TAT ACA TAT GGC ATG GCA TGG CCA CTG CAG GAT CCA CCA CCA TCA TCA TCA CGC ATC ACC ACC ACC 3' (SEQ ID NO:[16] 15)

pHis6R: 5' GAC GTC GCA TGC TTA CTC AGC TAG TGT GAT GGT GAT GAT GAT GGC CTA TGG TGG TGG TGG TGA TGC G 3' (SEQ ID NO:[17] 16)

Paragraph beginning at page 23, line 4, has been amended as follows:

c. The triple-ATG sequence and upstream region

5' TAATACGACTCACTATAGGGAGACCACAACGGTTTCCCTCTAG AAATAATTTTGTTTAACTTTAAGAAGGAGATATACATATGGCATGGCATGGC CA 3' (SEQ ID NO:[18] 17)

5' ATGGCATGGCATG 3' (SEQ ID [NO. 19] NO:18).

Paragraph beginning at page 26, line 24, has been amended as follows:

A fragment from pZL1 was PCR amplified using the primers ZL4 and ZL8 (SEQ ID NO:12 and 13). The primers ZL4 and ZL8 were designed with a *Nhe*I site or a *Bgl*II site at the 5' end, respectively. The PCR product was digested with *Nhe*I and *Bgl*II, and then ligated into

the pSlip2 vector that had been digested with *Nhe*I and *Bgl*II. The resulting vector is pSlip3. A fragment was obtained from pSlip3 by PCR using the primers ZL10 and ZL2 (SEQ ID NO:[14] 13 and 7). The resulting PCR product was digested with *Bgl*II and *Hin*dIII, then ligated back into *Bgl*II/*Hin*dIII-digested pSlip3 to generate pSlip4.

Paragraph beginning at page 27, line 1, has been amended as follows:

Plasmid pSlip4 was digested with *Mun*I and *Nhe*I. A T7 linker [(SEQ ID NO:15)], composed of these oligonucleotide sequences: 5' CTA GCC GAA ATT AAT ACG ACT CAC TAT AGG GAG AC 3' (SEQ ID NO:14) and 3' GG CTT TAA TTA TGC TGA GTG ATA TCC CTC TGT TAA 5' (SEQ ID NO:19), were synthesized. The linker, engineered such that the 5' terminus of each of the two strands either has a *Mun*I or a *Nhe*I 5' cohesive overhang, was ligated with the *Mun*I/*Nhe*I-digested pSlip4 vector to generate the pSlip7 vector.

The paragraph at page 1, lines 4-6 (amended in a preliminary amendment filed 1/27/04), has been replaced with the following:

-- This application is a divisional application and claims benefit under 35 U.S.C. 120 of U.S. Application No. 09/897,776, filed June 29, 2001, now U.S. Patent No. 6,709,863, which is a continuation-in-part application and claims benefit under 35 U.S.C. 120 of U.S. Application No. 09/732,990, filed December 8,

2000, now U.S. Patent No. 6,428,961, which claims benefit under 35 U.S.C. 119(e) of U.S. Application No. 60/169,725, filed December 8, 1999. --

In the claims:

At claim 21, line 12, -- and -- has been inserted immediately after "molecule;".

27. (Currently amended) A method for isolating a polypeptide encoded by a nucleic acid molecule, comprising:

~~e)~~ a) determining if said nucleic acid molecule encodes an open reading frame, using the method of ~~claim 21,~~ claim 21 and

~~f)~~ b) isolating said histidine tagged polypeptide.

32. (Currently amended) The method of claim 31, wherein said 13 nucleotides are ATGGCATGGCATG (SEQ ID ~~NO.19~~ NO:18).

33. (Currently amended) The method of claim 21, wherein said ~~isolated~~ nucleic acid sequence further comprises a ribosome-binding site positioned 5' of said start codons.

Information Disclosure Statement

The information disclosure statement filed 5/5/05, with regard to references AH-AK only, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the references have incomplete citations, e.g., no date is listed and no author is listed in the PTO-1449 form. It has been placed in the application file, but the information referred to therein (references AH-AK only) has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

The following is an examiner's statement of reasons for allowance:

Claims 21-25, 27, and 30-33 are drawn to a method for determining the presence or absence of an open reading frame in a nucleic acid molecule among a population of nucleic acid

molecules, the method comprising creating a nucleic acid vector comprising the nucleic acid molecule that comprises three start codons, one start codon in each of all three open reading frames, and a histidine tag in each of all three reading frames. The closest prior art is Amasino et al (Applicant reference AD). Although Amasino et al teaches a nucleic acid containing three ATG start codons in all three open reading frames, the reference by itself or with any other prior art, fails to teach or make obvious adding a histidine tag in each of the three open reading frames to the specific nucleic acid taught by Amasino et al, and using the resulting vector to determine the presence or absence of an open reading frame.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

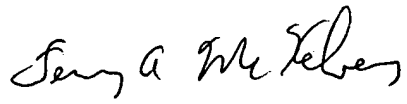
Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should

be directed to Terry A. McKelvey whose telephone number is (571) 272-0775. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

July 25, 2005